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Performance of advanced imaging modalities at diagnosis and treatment response evaluation of patients with post-transplant lymphoproliferative disorder: A systematic review and meta-analysis

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ABSTRACT

Introduction and aim: Post-transplant lymphoproliferative disorder (PTLD) is a serious complication after solid organ and hematopoietic stem cell transplantation, associated with significant morbidity and mortality. In this systematic review we evaluated the clinical performance of advanced imaging modalities at diagnosis and treatment response evaluation of PTLD patients after solid organ and hematopoietic stem cell transplantation.
Methods: We have carried out a literature search until December 15, 2017 using PubMed/Medline, Embase, "Web of Science" and Cochrane Library databases concerning the performance of computed tomography (CT), magnetic resonance imaging (MRI) and ^{18}F-flurodeoxyglucose positron emission tomography/computed tomography (FDG-PET/CT) at diagnosis or treatment response evaluation of PTLD patients.
Results: A total of 11 studies were included comprising 368 patients, from which FDG-PET(/CT) was the primary imaging modality investigated. The methodological quality according to QUADAS-2 of the reviewed studies was moderate-poor. Subgroup analysis of imaging results for detection and staging in patients with PTLD indicated that FDG-PET/(CT) identified additional lesions not detected by CT and/or MRI in 27.8%, (95% confidence interval [95%CI]) 17.0%–42.0% (I^2 = 51.1%), from which extra-nodal sites in 23.6% (95%CI: 7.9%–52.4%) (I^2 = 76.6%). False negative results occurred in 11.5% (95%CI: 4.9%–24.5%) (I^2 = 73.4%), predominantly in physiological high background activity regions and in early PTLD lesions. False positive results occurred in 4.8% (95%CI: 2.6%–8.6%) (I^2 = 0%) predominantly due to inflammatory conditions. Subgroup analysis of imaging results at treatment response evaluation indicated that FDG-PET(/CT) findings altered or guided treatment in 29.0% (95%CI: 14.0%–50.5%) (I^2 = 40.1%). False positive results during treatment response evaluation were reported in 20.0% (95%CI: 10.7%–34.2%) (I^2 = 0%), predominantly due to inflammatory conditions.
Conclusion: FDG-PET(/CT) is currently the most frequently investigated imaging modality in PTLD patients. Available studies report promising results in detection, staging and therapy evaluation but suffer from methodological shortcomings. Concerns remain with regard to occurrence of false negatives due to physiological high background activity and early PTLD lesions as well as false positives due to inflammatory conditions.

Abbreviations: BMB, bone marrow biopsy; CNS, central nervous system; CT, contrast enhanced computed tomography; DLBCL, diffuse large B-cell lymphoma; EBV, epstein Barr virus; FDG, ^{18}F-flurodeoxyglucose; MRI, magnetic resonance imaging; MTV, metabolic tumor volume; NPV, negative predictive value; PET, positron emission tomography; PPV, positive predictive value; PTLD, post-transplant lymphoproliferative disorder; QUADAS-2, quality Assessment of Diagnostic Accuracy Studies; R-CHOP, rituximab, cyclophosphamide, doxorubicin, vincristine and prednisolone; SUVmax, maximum standardized uptake value; TLG, total lesion glycolysis; WHO, World Health Organization

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1. Introduction

Post-transplant lymphoproliferative disorder (PTLD) is a serious complication after solid organ and hematopoietic stem cell transplantation, associated with high morbidity and mortality. Although initially reported as a rare complication of transplantation, PTLD incidence may have been clinically underestimated (Maksten et al., 2016). While lymphomas represent 4% of all cancers in an immunocompetent population, they account for 21% of all cancer cases in transplant recipients (Dierickx and Habermann, 2018). Incidence of PTLD may vary from 1 to 20% depending on various risk factors such as pre-transplant Epstein Barr virus (EBV) serology results, the degree of immunosuppression and the transplanted organ (Parker et al., 2010; Singavi and Fenske, 2015). In allogeneic hematopoietic stem cell transplantation, development of PTLD predominantly depends on the degree of human leukocyte antigen mismatch along with aggressive T-cell depletion methods (Landgren et al., 2009). PTLD encompasses a wide morphologic spectrum ranging from EBV driven polyclonal proliferation to highly aggressive monomorphic proliferations. Currently, the World Health Organization (WHO) categorizes PTLD into: (i) non-destructive lesions, (ii) polymorphic PTLD, (iii) monomorphic PTLD, and (iv) classical Hodgkin lymphoma type PTLD (Swerdlow et al., 2017). The most common is monomorphic PTLD, particularly diffuse large B-cell lymphoma (DLBCL) (Bakker et al., 2007; Styczynski, 2017; Mucha et al., 2010).

PTLD has an heterogeneous clinical presentation, which may resemble allograft dysfunction but may also be limited to nonspecific symptoms such as weight loss, fever or malaise. At diagnosis, the clinical spectrum ranges from a solitary asymptomatic process to a fulminant systemic disease (Singavi and Fenske, 2015; Koffman et al., 2000; Gottschalk et al., 2005). It may involve nodal and/or extra-nodal sites, including the organ allograft or any other organ system (Singavi and Fenske, 2015; Al-Mansour et al., 2013; Evens et al., 2010). PTLD may develop at any time with a first peak incidence within one year after transplantation and a second peak after 4–5 years (Bakker et al., 2007; Végso et al., 2011; Camacho et al., 2014; Everly et al., 2007). A variety of laboratory tests are routinely carried out to diagnose and monitor disease progression. In case of EBV-positive PTLD, pre-emptive treatment with rituximab is often initiated based on EBV DNA levels and its change is routinely monitored during treatment. However, a considerable limitation of this approach is the lack of standardized cutoff values, monitoring time points and sampling source (Dierickx and Habermann, 2018; Bakker et al., 2007; Styczynski, 2017). Although EBV-associated PTLD is more clinically recognized, the incidence of EBV-negative PTLD is often underestimated, comprising up to 50% of PTLD cases (Blaes and Morrison, 2010; Trappe et al., 2012; Luskin et al., 2015; Kinch et al., 2014). In light of such limitations, clinicians cannot solely rely on EBV values to monitor disease progression/regression. Upon suspicion of PTLD, a confirmatory biopsy provides essential histopathological information. However, this is an invasive procedure, may lead to complications and is not always possible for deep-seated lesions close to vital structures (Parker et al., 2010; Girometti et al., 2014).

Correct staging and accurate treatment response evaluation are vital, as treatment and prognosis depend on these factors (Panagiotidis et al., 2014). Considering the clinical characteristics of PTLD and the limitations of current methods, advanced imaging modalities play a crucial role at diagnosis and treatment response evaluation of PTLD patients. Established imaging modalities include contrast-enhanced computed tomography (CT) and magnetic resonance imaging (MRI), relying mainly on morphological information. In recent years, ^{18}F-flurodeoxyglucose (FDG) positron emission tomography (PET) and in particular hybrid FDG-PET/CT has gained clinical importance providing both functional and anatomic information.

This systematic review aims to provide an evidence-based guidance on the clinical value of advanced imaging modalities, including CT, MRI and FDG-PET/CT in patients with PTLD after solid organ and hematopoietic stem cell transplantation. The relevant literature was systematically reviewed with a focus on diagnosis and treatment response evaluation of patients with PTLD. The advantages and limitations of each individual imaging modality in the setting of PTLD are discussed. Future perspectives and suggestions for further research are also addressed.

2. Research design & methods

2.1. Selection criteria

The “PRISMA Statement for Reporting Systematic Reviews and Meta-Analysis” and its suggestions have served as template for this systematic review (Liberati et al., 2009; Moher et al., 2010). A systematic online literature search was conducted on PubMed/Medline, Embase, “Web of Science” with the search terms “lymphoproliferative disease/disorder”, “organ transplant”, “computed tomography”, “magnetic resonance imaging” and “^{18}F-FDG positron emission tomography” (for the full list of search terms, see Appendix 1). Data obtained through the database search until December 15, 2017 were used in this systematic review. Original articles concerning the performance of CT, MRI, FDG-PET or FDG-PET/CT at diagnosis and/or treatment response evaluation of PTLD after solid organ and hematopoietic stem cell transplantation were included. PTLD was classified according to the indications provided by the 2008 WHO classification: (i) early lesions, (ii) polymorphic PTLD, (iii) monomorphic PTLD, and (iv) classical Hodgkin lymphoma type PTLD (Swerdlow et al., 2008; Turner et al., 2010; Tsao and Hsi, 2007; Taylor et al., 2005). Although the authors acknowledge the existence of a revised version, the studies included in this systematic review were carried out before the current classification (Swerdlow et al., 2017). Both prospective and retrospective studies as well as blinded or non-blinded studies were included. There were no selection criteria based on a specific reference standard. Articles in English were considered. We excluded case reports/small case series (studies with less than 5 patients), pre-clinical studies, abstracts, conferences reports and seminar reports.

2.2. Literature search

Duplicates from the various online search databases were eliminated using Mendeley Desktop Version 1.1710 (Elsevier, Amsterdam, Netherlands). The remaining articles were screened for title and abstract. The selected articles were further evaluated in full-text for eligibility based on the inclusion criteria. Additionally, the Cochrane Library was searched for reviews on PTLD and crossed-checked references with selected studies for other relevant articles. The authors of the included studies were approached via email, when necessary, in an attempt to clarify results and obtain quantitative data.

2.3. Methodological quality assessment

Methodological quality of the included studies was assessed according to the “Quality Assessment of Diagnostic Accuracy Studies” (QUADAS-2) (Whiting et al., 2011). The four main assessment categories of QUADAS-2 include: patient bias, index test bias, reference test bias and flow and timing bias. CT, MRI or FDG-PET(/CT) were considered to be the index test. Although stand-alone FDG-PET studies were included in our systematic review, this technique is considered an outdated imaging modality and clinically inferior to FDG-PET/CT (Adams and Kwee, 2016a). The use of stand-alone FDG-PET was scored as high applicability concern. At diagnosis, histological confirmation of PTLD was considered to be the reference standard. At end of treatment, although histological confirmation was the preferred reference standard, biopsy is not always possible nor standardly requested by the treating physician. In case histological sampling was not available,

clinical follow-up for a minimum of 2 years and imaging was also accepted. The lack of a biopsy at treatment response evaluation may influence study bias, but not applicability to our review. A grading guideline was tailored for this systematic review to aid quality assessment (Appendix 2). For each category a quality grade was assigned ranging between: high risk of bias, unclear risk of bias or low risk of bias.

2.4. Statistical analysis

Pooled subgroup analyses were performed for mutual denominators among the included studies. In the detection and staging sections these were: detection of additional lesions, detection of extra-nodal lesions, upstaging of patients, clarification of dubious lesions, false negative and false positive results. In the treatment response evaluation section the subgroups were: detection of additional lesions, early remission detection, influence on treatment course, additional guidance in therapy monitoring, false negative results, false positive results and relapse after complete remission according to FDG-PET(/CT). An I^2 greater than 50% was considered indicative of high inter-study heterogeneity (Higgins et al., 2003). Weighted proportions with a 95% confidence interval (CI) were calculated using a random effects model ($I^2 > 50\%$) or a fixed effects model ($I^2 \leq 50\%$). Statistical analyses were executed using Comprehensive Meta-Analysis Version 3 (Biostat, Englewood, Illinois, USA).

3. Results

3.1. Selection of literature

After duplicate exclusion, a total of 4619 articles were identified through an electronic database literature search (Fig. 1). After reviewing these articles for title and/or abstract, 27 FDG-PET(/CT), 16 CT and 16 MRI articles remained. These were further analyzed in full-text. Sixteen FDG-PET(/CT) articles were excluded: 5 reported results in less than 5 patients, 3 articles included non-separable data from other complications after organ transplantation, 5 were pictorial or descriptive studies, in 2 articles PTLD was not the main focus of the discussion and 1 article included histopathology results not concurrent with the 2008 WHO classification of PTLD. In total, 11 FDG-PET(/CT) articles were included in this review. Only 1 article on the diagnostic performance of CT remained after full-text evaluation. The majority of excluded articles did not provide any information regarding the performance of CT in the evaluation of PTLD patients (n = 11). Of the 4 remaining studies, 2 articles included histopathology results not concurrent with the 2008 WHO classification, 1 included less than 5 patients, and in 1 article data from other immunocompromised patients could not be separated from PTLD. No article concerning MRI could be included in this review. Five articles included less than 5 patients and another 6 were pictorial or descriptive studies. The remaining 5 studies did not provide any original data. In total, this review included 11 original research articles because 1 article reported the diagnostic performance of both FDG-PET/CT and CT alone.

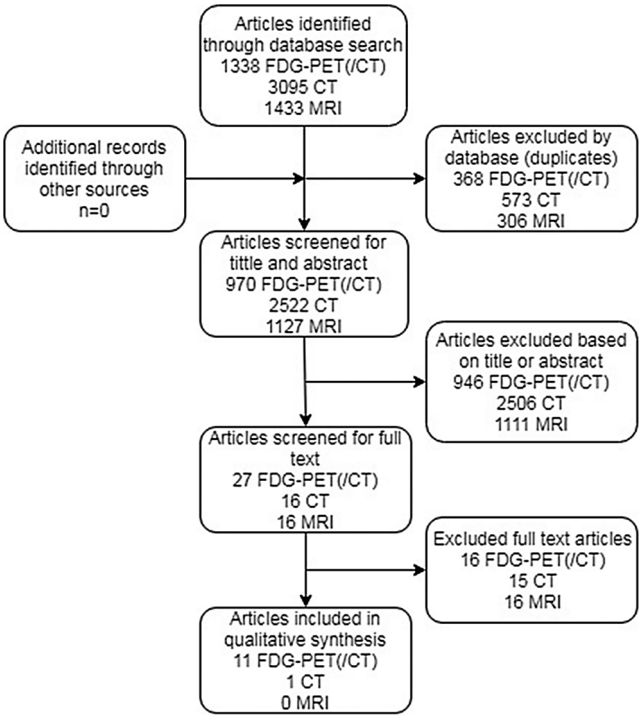

Fig. 1. Study selection flow-chart.

3.2. Methodological quality of included studies

The methodological quality of included studies according to QUADAS-2 is displayed in Table 1 and Fig. 2. With regard to patient selection, 4 studies had a high risk of bias and 6 high applicability concerns. Concerns leading to high risk of bias classification included: clinical diagnosis of PTLD in a significant number of patients and inappropriate exclusions. Applicability concerns were due to a narrow study population. In the index test domain 7 studies scored unclear risk of bias because these studies did not report if FDG-PET(/CT) was interpreted in a blinded fashion and 1 study scored high risk of bias because of non-blinded interpretation. Seven studies had high applicability concerns with regard to the index test. These studies either used stand-alone FDG-PET in the evaluation of PTLD patients or outdated interpretation criteria for FDG-PET(/CT) scans. With regard to the reference standard, 9 studies scored high risk of bias because findings on FDG-PET(/CT) were not systematically histologically confirmed either at diagnosis or follow-up. High application concerns for reference index were scored in 3 studies. In 2 studies, follow-up was less than 2 years after the last FDG-PET(/CT) scan and in 1 study there was no clear reference standard. Nine studies had high risk of bias with regard to flow and timing. The main concerns were lack of baseline FDG-PET(/CT) and inconsistent/lack of a reference standard.

3.3. Study characteristics

The 11 studies included in this systematic review compromised a total of 368 patients. Each patient included in the review underwent at least one FGD-PET(/CT) scan performed at diagnostic or treatment response evaluation of PTLD (Table 2) (Panagiotidis et al., 2014; Blaes et al., 2009; Zimmermann et al., 2018; von Falck et al., 2007; Dierickx et al., 2013; Gheysens et al., 2016; Guerra-García et al., 2017; Bakker et al., 2006; O'Conner and Franc, 2005; Takehana et al., 2014; Vali et al., 2015). The age of participants ranged from 1 to 82 years. Three studies used solely stand-alone FDG-PET, 4 studies used stand-alone FDG-PET and FDG-PET/CT and 4 studies used exclusively FDG-PET/CT. In the 269 histologically proven PTLD cases at diagnosis, the majority of PTLD lesions were of the monomorphic subtype (n = 215), followed by polymorphic (n = 24), early lesions (n = 21) and classical Hodgkin lymphoma type PTLD (n = 9). In the remaining cases, diagnosis of PTLD was based on clinical findings or follow-up. The type of transplantations most frequently performed in our study cohort were: kidney (35%) followed by liver (19%), lung (15%), heart (13%), hematopoietic stem cell transplantation (9%), multiorgan transplant (6%), small bowel (2%) and pancreas (1%).

3.4. Role of imaging in detection and staging

Ten studies provided data about the diagnostic and staging

Table 1
Risk of bias in different domains according to the QUADAS-2.

Study (year)	Risk of bias				Applicability concerns		
	Patient selection	Index test	Reference standard	Flow and Timing	Patient selection	Index test	Reference standard
Bakker et al. (2006)	Low	Unclear	High	High	High	High	Low
Blaes et al. (2009)	Low	Unclear	High	High	Low	High	Low
von Falck et al. (2007)	High	Unclear	High	High	High	High	High
Dierickx et al. (2013)	High	Low	High	High	Low	High	Low
Gheysens et al. (2016)	Low	Low	High	High	High	Low	High
Guerra-García et al. (2017)	Low	Unclear	High	High	High	Unclear	Low
O'Conner and Franc (2005)	Low	Unclear	High	High	High	High	Unclear
Panagiotidis et al.(2014)	High	High	High	High	Low	Low	High
Takehana et al. (2014)	Low	Unclear	Low	Low	Low	Low	Low
Vali et al. (2015)	Low	Low	Low	Low	High	High	Low
Zimmermann et al. (2018)	High	Unclear	High	High	Low	High	Low

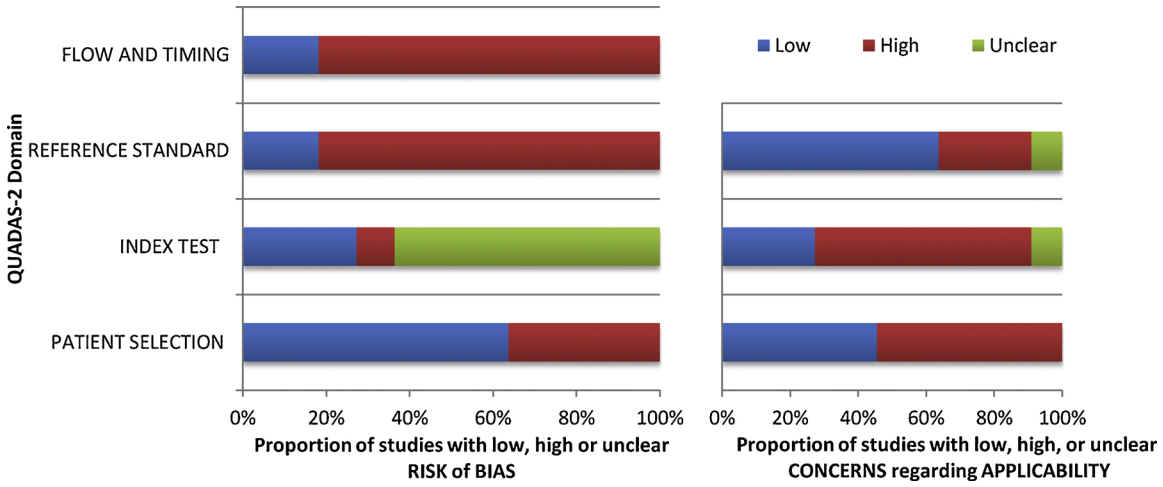

Fig. 2. Risk of bias in different domains according to the QUADAS-2.

performance of FDG-PET(/CT) (Table 3) (Table 4) (Panagiotidis et al., 2014; Blaes et al., 2009; von Falck et al., 2007; Dierickx et al., 2013; Gheysens et al., 2016; Guerra-García et al., 2017; Bakker et al., 2006; O'Conner and Franc, 2005; Takehana et al., 2014; Vali et al., 2015). Pooled data from 7 studies showed that FDG-PET(/CT) identified additional lesions in 27.8% (95%CI: 17.0%–42.0%) (I^2 = 51.1%) not detected by morphological imaging (CT or MRI), from which extra-nodal sites in 236% (95%CI: 7.9%–52.4%) (I^2 = 76.6%) (Panagiotidis et al., 2014; Blaes et al., 2009; von Falck et al., 2007; Bakker et al., 2006; Dierickx et al., 2013, 2013; Gheysens et al., 2016; Guerra-García et al., 2017; Bakker et al., 2006; O'Conner and Franc, 2005; Takehana et al., 2014; Vali et al., 2015). Based on 3 studies, FDG-PET/CT findings upstaged patients compared to CT alone in 15.3% (95%CI: 9.0%–24.7%) (I^2 = 100%). Data from 4 studies indicated that FDG-PET(/CT) was used to clarify dubious lesions seen on morphological imaging in 29.1% (95%CI: 7.5%–67.4%) (I^2 = 70.2%) (Panagiotidis et al., 2014; Blaes et al., 2009; Takehana et al., 2014; Vali et al., 2015). Using available data from 4 studies, it could be demonstrated that FDG-PET(/CT) failed to detect histologically confirmed PTLD lesions in 11.5% (95%CI: 4.9%–24.5%) (I^2 = 73.4%) (Panagiotidis et al., 2014; Blaes et al., 2009; Dierickx et al., 2013; Vali et al., 2015). These, particularly involved regions of physiological high background activity, such as the brain, kidneys or heart and early PTLD lesions. In a single study, CT detected additional lesions not visualized on stand-alone FDG-PET in 7 cases (Vali et al., 2015). Based on 2 studies, false positive results at staging were observed in 4.8% (95%CI: 2.6%–8.6%) (I^2 = 702%), predominantly due to inflammatory conditions (Panagiotidis et al., 2014; Dierickx et al., 2013). Data extracted from 2 studies indicated that patient-based sensitivity of FDG-PET(/CT) varied between 88–89%, specificity between 89–91%, positive predictive value (PPV) between 88–91% and negative predictive value (NPV) between 87–91% (Panagiotidis et al., 2014; Dierickx et al., 2013). Concerning CT, Panagiotidis et al. found a sensitivity of 88%, specificity of 89%, PPV of 88% and NPV of 89% (Panagiotidis et al., 2014).

Gheysens et al. focused exclusively on the diagnostic performance of FDG-PET/CT for the detection of bone marrow involvement in PTLD patients compared to bone marrow biopsy (BMB). Although false-positive results could not be completely ruled out, FDG-PET/CT was reported to have higher sensitivity than BMB in detecting bone marrow involvement (Gheysens et al., 2016). These findings seem to be supported by other included studies, where FDG-PET(/CT) was an accurate tool in detecting bone marrow lesions (Panagiotidis et al., 2014; von Falck et al., 2007; O'Conner and Franc, 2005; Takehana et al., 2014; Vali et al., 2015). The clinical value of the maximum standardized uptake value (SUVmax) and its ability to distinguish between different PTLD subtypes was also evaluated. Takehana et al. found a statistically significant difference in the mean SUVmax between PTLD subtypes, reporting a mean SUVmax for the monomorphic subtype of 10.9 versus 4.5 for the polymorphic type (Takehana et al., 2014). In the study by Vali and colleagues, the mean SUVmax for monomorphic PTLD was 8.9, while the values for polymorphic and early subtypes were 5.1 and 4.8, respectively. However, this difference was not statistically significant (Vali et al., 2015).

3.5. Role of imaging in treatment response evaluation

A total of 6 studies evaluated the performance of FDG-PET(/CT) either at interim or end of treatment (Tables 5 and 6) (Blaes et al., 2009;

Table 2
Characteristics of included studies investigating advanced imaging modalities in patients with PTL.

Study (year)	Total № of patients	Mean age in years (range)	Type of scan	Histology at diagnosis	Transplanted organ
Bakker 2006	12	NA	Stand-alone FDG-PET	NA	12 Kidney
Blaes, 2009	19	42 (3–65)	Stand-alone FDG-PET	17 Monomorphic PTLD (16 DLBCL, 1 T-cell lymphoma) 1 Polymorphic PTLD 1 Hodgkin-like PTLD	6 Multiorgan 4 Lung 4 Kidney 2 Liver 2 HSCT 1 Bowel
Dierickx 2013*	150 № of scans 170	NA	Stand-alone FDG-PET (n = 73) FDG-PET/CT (n = 97)	76 Monomorphic PTLD (64 DLBCL, 12 non-DLBCL) 3 Polymorphic PTLD 11 Early lesions 3 Hodgkin-like PTLD 77 Not performed	51 Kidney 23 Liver 22 Lung 22 Heart 22 HSCT 8 Multiorgan 2 Bowel
von Falck, 2007	7	7 (3–13)	Stand-alone FDG-PET (n = 2) FDG-PET/CT (n = 5)	6 Monomorphic PTLD (4 DBCL, 1 T-cell lymphoma, 1 Burkitt-like PTLD) 1 Polymorphic PTLD	4 Kidney 2 Heart 1 Multiorgan
Gheysens, 2016	25	42 (6–76)	FDG-PET/CT	21 Monomorphic PTLD (17 DLBCL, 2 plasmablastic lymphoma, 1 T-cell lymphoma, 1 Burkitt-like PTLD) 2 Polymorphic PTLD 2 early lesion	10 Kidney 10 Lung 2 Heart 2 Liver 1 Multiorgan
Guerra-Garcia 2017	9	8 (1–18)	FDG-PET/CT	8 Monomorphic PTLD (4 DLBCL, 4 Burkitt-like PTLD) 1 Polymorphic PTLD	6 Liver 2 HSCT 1 Kidney
O'conner 2005	5	21 (10–39)	Stand-alone FDG-PET (n = 4) FDG-PET/CT (n = 1)	4 Monomorphic PTLD 1 Early lesions	5 Kidney
Panagiotidis 2014	40	52 (11–77)	FDG-PET/CT	13 Monomorphic PTLD (12 DLBCL, 1 plasmablastic lymphoma 1 Hodgkin-like PTLD 26 Not performed	16 Liver 16 Kidney 4 Heart 1 Pancreas 1 Multiorgan 1 HSCT 1 Lung
Takehana 2014	30	24 (2–77)	FDG-PET/CT	18 Monomorphic PTLD (16 DLBCL, 2 T-cell lymphoma) 5 Polymorphic PTLD 4 Hodgkin-like PTLD 3 Not performed	7 Liver 6 Kidney 3 Bowel 5 Heart 5 Lung 3 HSCT 1 Multiorgan
Vali 2015	34	10 (4–17)	Stand-alone FDG-PET	19 Monomorphic PTLD (14 DLBCL, 2 Burkitt-like PTLD, 3 T-cell lymphoma) 7 Polymorphic PTLD 7 Early lesions 1 Not performed	13 Heart 8 Lung 4 Kidney 3 Liver 3 Multiorgan 3 HSCT
Zimmermann 2017	37	54 (20–82)	Stand-alone FDG-PET (n = 4) FDG-PET/CT (n = 33)	33 Monomorphic (26 DLBCL, 3 Burkitt-like PTLD, 4 NA) 4 Polymorphic	17 Kidney 12 Liver 4 Lung 2 Heart 2 Multiorgan

Abbreviations: CT computed tomography; DLBCL Diffuse large B-cell lymphoma; HSCT Hematopoietic stem cell transplantation; NA not available; PET 18 F-flurodeoxyglucose positron emission tomography; PTLD Post-transplant lymphoproliferative diseases.
* Results "Type of scan" and "Histology at diagnosis" per number of scans; results per patient not available.

Zimmermann et al., 2018; von Falck et al., 2007; Guerra-García et al., 2017; Bakker et al., 2006; O'Conner and Franc, 2005). Pooled data from 3 studies showed that FDG-PET(/CT) detected additional lesions not visualized by CT in 15.0% (95%CI: 5.7%–34.1%) (I^2 = 0%), leading to intensification or continuation of treatment (Blaes et al., 2009; Guerra-García et al., 2017; Bakker et al., 2006). Data from 3 studies indicated that after initial treatment, lesions detected on CT were metabolic inactive on FDG-PET(/CT) in 32.1% (95%CI: 15.9%–54.2%) (I^2 = 0%) (von Falck et al., 2007; Guerra-García et al., 2017; Bakker et al., 2006). In these studies, patients with inactive metabolic lesions on FDG-PET(/CT) were considered to be in complete remission and treatment was stopped in half of the cases to minimize treatment related complications. Patients in which treatment was stopped remained in complete remission throughout study follow-up (Guerra-García et al., 2017; Bakker et al., 2006). Based on 3 studies, findings from FDG-PET(/CT) influenced treatment course in 29.0% (95%CI: 14.0%–50.5%) (I^2 = 40.1%) (Blaes et al., 2009; Guerra-García et al., 2017; Bakker et al., 2006). Furthermore, data from 3 studies indicated that FDG-PET(/CT) provided additional support in therapy guidance in 13.5% (95%CI: 4.3%–35.1%) (I^2 = 0%) by aiding the visualization of disease progression/remission (Blaes et al., 2009; Guerra-García et al., 2017; O'Conner and Franc, 2005). False negative results were reported in one study, in a single case of central nervous system (CNS) involvement (Guerra-García et al., 2017). Pooled data from 2 studies showed that false positive results during treatment response evaluation occurred in 20.0% (95%CI: 10.7%–34.2%) (I^2 = 0%), predominantly due to inflammatory conditions. Based on 2 studies, 12.4% (95%CI: 5.2%–27.0%) (I^2 = 65.0%) of patients relapsed during study follow-up after complete remission according to FDG-PET(/CT) scans.

In a 5-year follow-up study, Zimmerman et al. reported an end of treatment FDG-PET(/CT) sensitivity of 71%, a specificity 73%, a PPV 38% and an NPV 92% for PTLD relapse. Additionally, a negative end of treatment FDG-PET(/CT) was found to be a predictor of longer progression-free survival and longer time to progression (p = 0.013 and p = 0.019) (Zimmermann et al., 2018). These findings were replicated by Bakker et al., in which stand-alone FDG-PET was reported to be a predictor of progression-free survival (Bakker et al., 2006).

4. Discussion

This systematic review and meta-analysis evaluated the clinical performance of advanced imaging modalities in diagnosis and treatment response evaluation of PTLD patients after solid organ and hematopoietic stem cell transplantation. In the selected studies, FDG-

Table 3
Overview imaging results for the detection and staging of patients with PTLD.

Study (year)	№ of patients/ scans	Reference standard	Diagnostic & staging performance		Additional findings
			Benefit	Cautions	
Bakker 2006	10/10	Histology	In 5 events PET detected lesions not visualized by CT, from which in 5 events extra-nodal lesions		All biopsy sites were PET-avid regardless of PTLD subtype
Blaes 2009	17/17	Histology	In 1 event PET detected lesions not visualized by CT. Upstaging of disease in 1 event	In 3 events PET was false negative, from which 2 events of CNS involvement visualized by CT and MRI and 1 event of focal BMI	All biopsy sites were PET-avid regardless of PTLD subtype
Dierickx 2013	150/170	Histology (70%) Clinical findings/ imaging (30%)	Center and format as follow: Se 89%, Sp 89%, PPV 91%, NPV 87% FP: infections or inflammatory conditions (n = 6), NA (n = 2) FN: early lesions (n = 4) from which n = 2 isolated kidney and heart graft localization respectively, DLBCL (n = 3), CNS PTLD (n = 2), HL (n = 1)		
von Falck 2007	5/5	Histology	In 1 event PET detected lesions not visualized by CT and MRI In 3 events PET clarified dubious lesions visualized on CT and/or MRI		All biopsy sites were PET-avid regardless of PTLD subtype PET had no additional value in staging according to ST. Judes pediatric NHL
Gheysens, 2016	25/25	BMB/Imaging			Detection of BMI: In 6 events PET had a better diagnostic performance than BMB in detecting BMI
Guerra-Garcia 2017	6/6	Histology	In 1 event PET clarified a dubious lesion visualized on CT		All biopsy sites were PET-avid regardless of PTLD subtype
O'conner 2005	5/5	Histology	In 2 events PET detected lesions not visualized by CT In 3 events PET clarified dubious lesions visualized on CT		All biopsy sites were PET-avid regardless of PTLD subtype
Panagiotidis 2014	40/40	Histology (n = 14) Clinical findings (follow-up)/imaging (n = 26)	In 5 events PET detected lesions not visualized by CT, from which in 3 events with extra-nodal lesions. Upstaging of disease in 5 events Se 88%, Sp 91%, PPV 88%, NPV 91% FP: infection of native kidney (n = 1), malignant melanoma (n = 1) FN: NA		Detection performance CT: Se 88%, Sp 89%, PPV 88%, NPV 89%
Takehana 2014	30/30	Histology (n = 27) Clinical findings/ imaging (n = 3)	In 10 events PET detected lesions not visualized by CT and/or MRI, from which in 8 events extra-nodal lesions In 2 events PET clarified a dubious lesions visualized on CT		All biopsy sites were PET-avid regardless of PTLD subtype SUVmax(mean): polymorphic 4.5, monomorphic 10.9, HL type 6.4 ($p < 0.05$)
Vali 2015	34/34	Histology (n = 33) Clinical findings/ imaging (n = 1)	In 13 events PET detected lesions not visualized by CT. Upstaging of disease in 7 events In 2 events PET clarified dubious lesions visualized on CT	In 7 events PET was false negative, from which 3 events in the tonsils, 1 in the soft palate, 1 in the bowel, 2 in mesenteric and cervical lymph nodes) In 7 events CT detected lesions not visualized by PET	PET detected more lesions in the bone/bone marrow and smaller lymph nodes than CT CT detected more lesions in stomach and bowel than PET SUVmax(mean): early 4.8, polymorphic 5.1, monomorphic 8.9 (p = 0.11). SUVmax(mean) had no correlation with EBV viral load PET may be used to guide biopsies

Abbreviations: BMB: Bone marrow biopsy; BMI: bone marrow involvement; CNS: central nervous system; CT: computed tomography; DLBCL: Diffuse large B-cell lymphoma, EBV: Epstein Barr virus; FN: false negative; FP: false positive; HL; Hodgkin lymphoma; MRI: magnetic resonance imaging; NA: not available; NPV: negative predictive value; PET: 18F-flurodeoxyglucose positron emission tomography/(computed tomography); PPV: positive predictive value; PTLD: Post-transplant lymphoproliferative disorder; Se: sensitivity; Sp: Specificity; SUVmax: maximum standardized uptake value.

Table 4
Subgroup analysis of imaging results for detection and staging in patients with PTLD (n = 317).

	Detection of additional lesions	Detection of additional extra-nodal lesions	Upstaging of patients	Clarification of dubious lesions	False negative	False positive
Number of studies	7	3	3	5	4	2
Pooled summary analysis proportion (95% CI)	27.8% (17.0%–42.0%)	23.6% (7.9%–52.4%)	15.3% (9.0%–24.7%)	29.1% (7.5%–67.4%)	11.5% (4.9%–24.5%)	4.8% (2.6%–8.6%)
I2-statistic	51.1%	76.6%	100%	70.2%	73.4%	0%

PET(/CT) identified at diagnosis additional metabolic foci not visualized by morphological imaging in 27.8% (95%CI: 17.0%–42.0%) (Panagiotidis et al., 2014; Blaes et al., 2009; von Falck et al., 2007; Dierickx et al., 2013; Gheysens et al., 2016; Guerra-García et al., 2017; Bakker et al., 2006; O'Conner and Franc, 2005; Takehana et al., 2014; Vali et al., 2015). Detection performance was relatively high with reported sensitivity values between 88%–89% and specificity between 89%–91%. Reported PPV and NPV values were as high as 91% (Panagiotidis et al., 2014; Dierickx et al., 2013). Similar detection performance of CT was reported by 1 reviewed study (Panagiotidis et al., 2014). At treatment response evaluation FDG-PET(/CT) findings altered or provided additional treatment guidance in 29.0% (95%CI: 14%–50.5%) (Blaes et al., 2009; von Falck et al., 2007; Guerra-García et al., 2017; Bakker et al., 2006; O'Conner and Franc, 2005). End of treatment FDG-PET(/CT) as a predictor for relapse had moderate sensitivity of 71%, a moderate specificity 73%, but a satisfactory NPV of 92%. Finally, a negative end of treatment FDG-PET(/CT) was reported to be a predictor of longer progression-free survival in 2 studies (Zimmermann et al., 2018; Bakker et al., 2006).

Despite histopathologic similarities between PTLD and other lymphoid malignancies, direct extrapolation of research results from other hematological malignancies is not possible as pathogenesis, clinical presentation and management of PTLD differs significantly from that of lymphomas seen in immunocompetent patients (Ganne et al., 2003). Nonetheless, guidelines initially developed for staging and response assessment of other lymphoid malignancies are commonly applied to PTLD. In the evaluation of other FDG-avid lymphoproliferative malignancies, FDG-PET/CT has become standard procedure, yet its role in PTLD is less well defined (Cheson, 2015; Barrington et al., 2014; Juweid, 2011).

The results from this systematic review indicate that FDG-PET(/CT) plays an important role in diagnosis, staging and treatment response evaluation of patients with PTLD. At diagnosis, accurate staging is crucial as it determines extent of disease, prognosis and serves as a baseline in treatment response evaluation. FDG-PET(/CT) detected additional lesions not readily visualized by morphological imaging, particularly extra-nodal lesions in 23.6% (95% CI: 7.9%–52.4%) of cases (Panagiotidis et al., 2014; Bakker et al., 2006; Takehana et al., 2014) (Fig. 3). Morphologic features may be nonspecific and the visualization of metabolic areas may be crucial in differentiating between benign from malignant processes (Kwee et al., 2008; Juweid and Cheson, 2005). Additional lesions detected by FDG-PET(/CT) may lead to upstaging of disease and have a consequent clinical impact. Because PTLD is characterized by an high incidence of extra-nodal involvement, FDG-PET(/CT) may be more suitable than CT and/or MRI in diagnosis and staging of these patients (Dierickx and Habermann, 2018; Scarsbrook et al., 2005). Regarding treatment response evaluation, FDG-PET(/CT) findings influenced treatment course in 29.0% (95% CI: 14.0%–50.5%), including cessation of treatment supported by metabolic complete remission according to FDG-PET/CT (Blaes et al., 2009; Guerra-García et al., 2017; Bakker et al., 2006). FDG-PET(/CT) may be crucial in the visualization of metabolic inactive lesions and improve treatment stratification decisions (Fig. 4). The current mainstay of treatment for PTLD patients not responding to reduction of immune suppression and/or initial rituximab therapy is R-CHOP (rituximab, cyclophosphamide, doxorubicin, vincristine and prednisolone) as second line treatment. Especially in patients with solid organ transplant this is a highly toxic regimen, contributing to high treatment morbidity and mortality (Singavi and Fenske, 2015; Dierickx et al., 2015; Choquet et al., 2007; Elstrom et al., 2006). The treating physician is therefore faced with the difficult decision of weighting treatment benefit against the risk of treatment related complications. The results of this systematic review elucidate the value of FDG-PET(/CT) in therapy management with the potential to diminish treatment burden. Furthermore, a negative FDG-PET(/CT) at end of treatment increases the likelihood that PTLD is in clinical remission (NPV 92%) and patients may enter standard clinical follow-up. On the other hand, considering the unsatisfactory PPV, a positive FDG-PET(/CT) at the end of treatment may require further diagnostic work-up (Zimmermann et al., 2018)

FDG-PET/CT has however certain drawbacks as the main imaging modality. Regions of high background activity such as the brain, myocardium, gastro-intestinal tract, bone marrow recovering from chemotherapy and excretion of FDG through the urinary tract may hinder an accurate diagnosis (Kwee et al., 2008; Yeung et al., 2003; Lauro et al., 2015; Zukotynski et al., 2012). Caution is warranted in the evaluation of heart, kidney and bowel transplant patients considering that involvement of the transplanted organ occurs in up to 50% of PTLD cases (Lopez-Ben et al., 2000; Opelz and Döhler, 2004). Another point of concern is the high frequency of CNS involvement, which may occur in 5–20% of PTLD cases (Dierickx and Habermann, 2018; Singavi and Fenske, 2015; Caillard et al., 2006). Our review has demonstrated that FDG-PET(/CT) is not accurate in detecting CNS lesions in PTLD patients, missing the diagnosis in multiple occasions (Blaes et al., 2009; Dierickx et al., 2013; Guerra-Garcöa et al., 2017). These findings are concurrent with current lymphoma and PTLD guidelines which recommend the use of MRI to assess suspicion of CNS involvement (Parker et al., 2010; Barrington et al., 2014). In addition to areas of high background activity, false negative results may also occur due the limited spatial resolution of 6–7 mm of the PET/CT camera system. Although high-grade lymphomas are well visualized with FDG-PET/CT, concerns still remain in low-grade histological subtypes (Elstrom et al., 2003; Noraini et al., 2009). Given the histological variability of PTLD, the diagnostic performance of FDG-PET/CT may be reduced in indolent types. The results from our review indicate that while PTLD lesions were generally FDG-avid, concerns still remain in early-lesion PTLD (Panagiotidis et al., 2014; Dierickx et al., 2013).

FDG-PET/CT may also lead to false positive results due to inflammatory reactions. Concerns about the high incidence of false positive results with FDG-PET/CT are reported in other hematological malignancies (Adams and Kwee, 2016a, b). Adams et al. have carried out a systematic review and concluded that FDG-PET scans in patients with lymphoma suffer from a high number of false positives during and after treatment completion (Adams and Kwee, 2016a). According to the author, proportion of false positives during and after treatment may range between 7.7 and 90.5%, mainly due to inflammatory conditions. This high rate of false positives may lead to unnecessary continuation of highly toxic treatment, with high treatment-related mortality and an increased chance of graft dysfunction and graft loss in transplant patients. In the reviewed cases, several results were reported as false positives, mainly due to inflammatory conditions. However, due to the lack of histological confirmation and lack of data, no firm conclusion can be made about the incidence of FDG-PET/CT false positive results

Table 5
Overview imaging results for treatment response evaluation in patients with PTLD.

Study (year)	№ of patients/ scans	Mean follow-up (months)	Reference standard	Treatment response evaluation performance		Additional findings
				Benefit	Cautions	
Bakker, 2006	7/NA	37 (2–46)	Clinical findings/ imaging	End of treatment In 1 event PET detected lesions not visualized by CT. Altered treatment In 1 event PET demonstrated remission earlier than CT. Altered treatment		Negative end of treatment PET was predictor of longer progression-free survival
Blaes 2009	13/22	12 (5–50)	Clinical findings/ imaging	Interim & end of treatment In 1 event PET detected lesions not visualized by CT. Altered treatment	In 3 events relapse after CR with PET	Interim PET provided additional guidance in therapy monitoring (n = 1)
von Falck 2007	7/12	9	Clinical findings/ imaging	Interim & end of treatment In 3 events PET demonstrated remission earlier than CT and/or MRI		
Guerra-Garcia 2017	9/14	74 (12–181)	Clinical findings/ imaging (n = 4) Histology (n = 5)	Interim In 2 events PET detected lesions not visualized by CT. Altered treatment (n = 1) In 3 events PET demonstrated remission earlier than CT. Altered treatment	In 1 event PET was false negative, from which 1 event of CNS involvement visualized by MRI In 1 event PET was false positive, attributed to treatment related inflammation (n = 1)	PET concurrent with clinical CR in 6 events PET provided additional guidance in therapy monitoring (n = 1).
O'conner 2005	3/NA	NA	Clinical findings/ imaging			Interim PET provided additional guidance in therapy monitoring (n = 1)
Zimmermann 2017*	37/NA	60	Clinical findings/ imaging	End of treatment Se 71%, Sp 73%, PPV 38%, NPV 92% FP: inflammatory conditions (n = 3), NA (n = 5)	In 2 events relapse after CR with PET	Negative end of treatment PET was predictor of longer progression-free survival and time to progression

Abbreviations: CNS: central nervous system; CR: complete remission; CT: computed tomography; NA: not available; FP: false positive; FN: False negative; NPV: negative predictive value; MRI: magnetic resonance imaging; PET: 18F-flurodeoxyglucose positron emission tomography/(computed tomography); PPV: positive predictive value; Se: sensitivity; Sp: Specificity; SUVmax: maximum standardized uptake value.

Table 6
Subgroup analysis of imaging results for treatment response evaluation in patients with PTLD (n = 76).

	Detection of additional lesions	Early remission detection	Influence on treatment course	Additional guidance in therapy monitoring	False negative	False positive	Relapse after PET complete remission
Number of studies	3	3	3	3	1	2	2
Pooled summary analysis proportion (95% CI)	15.0% (5.7%–34.1%)	32.1% (15.9%–54.2%)	29.0% (14.0%–50.5%)	13.5% (4.3%–35.1%)	11.5% (4.9%–24.5%)	20.0% (10.7%–34.2%)	12.4% (5.2%–27.0%)
I2-statistic	0%	0%	40.1%	0%	–	0%	65.0%

in PTLD patients. Although Zimmermann et al. and Panagiotidis et al. have argued that false positive results may lead to the identification and treatment of other potentially life threatening conditions, these may also lead to invasive biopsies or other additional interventions with associated complications (Panagiotidis et al., 2014; Zimmermann et al., 2018).

5. Limitations

The heterogeneity of the reviewed studies makes direct comparison challenging. Heterogeneity across the included studies must be taken into consideration when interpreting the polled subgroup analyses. Six out of the 12 subcategories were considered to have high inter-study heterogeneity, particularly the subcategory “upstaging of patients”. Population size and characteristics were heterogeneous across studies, as well as methodology. Some studies used stand-alone FDG-PET as their main imaging modality while others used FDG-PET/CT. Additionally, acquisition methods for imaging modalities were often partially described and varied per study group. Such details influence diagnostic image quality and as result diagnostic accuracy. Interpretation of FDG-PET(/CT) across studies was heterogeneous and/or minimally described. The Deauville criteria are nowadays standardly applied in treatment response evaluation of lymphomas, however several studies included in this systematic review were carried out before standardization occurred (Barrington et al., 2014). The methodology of the reviewed studies was moderate-poor. Key concerns included: lack of histological confirmation of suspected lesions (particularly at follow up), inconsistent reference standard and the use of stand-alone FDG-PET (Parker et al. (2010); Fueger et al. (2009)). The lack of histological confirmation is also a major drawback in the reviewed studies. Considering the potential for false negative and false positive results with FDG-PET/CT, a confirmatory biopsy would have strengthened the conclusions drawn by the reviewed studies. Although it is clinically accepted and understood that histological confirmation is not always possible in clinical practice, its lack in this context, diminishes the degree of certainty of the conclusions in the context of this systematic review. Lastly, the lack of studies focusing on stand-alone CT or MRI for diagnosis and treatment response evaluation in PTLD makes intermodal comparison impossible.

6. Future perspectives

Although the importance of FDG-PET/CT is well established in the field of hematological malignancies, this is not yet the case in PTLD patients and international prospective studies are recommended to compare the performance of the different imaging modalities. Specifically, studies which evaluate the performance of FDG-PET/CT at interim and end of treatment are lacking. These studies may additionally evaluate the ability of FDG-PET/CT to improve risk stratification of patients during treatment. Although no MRI studies were

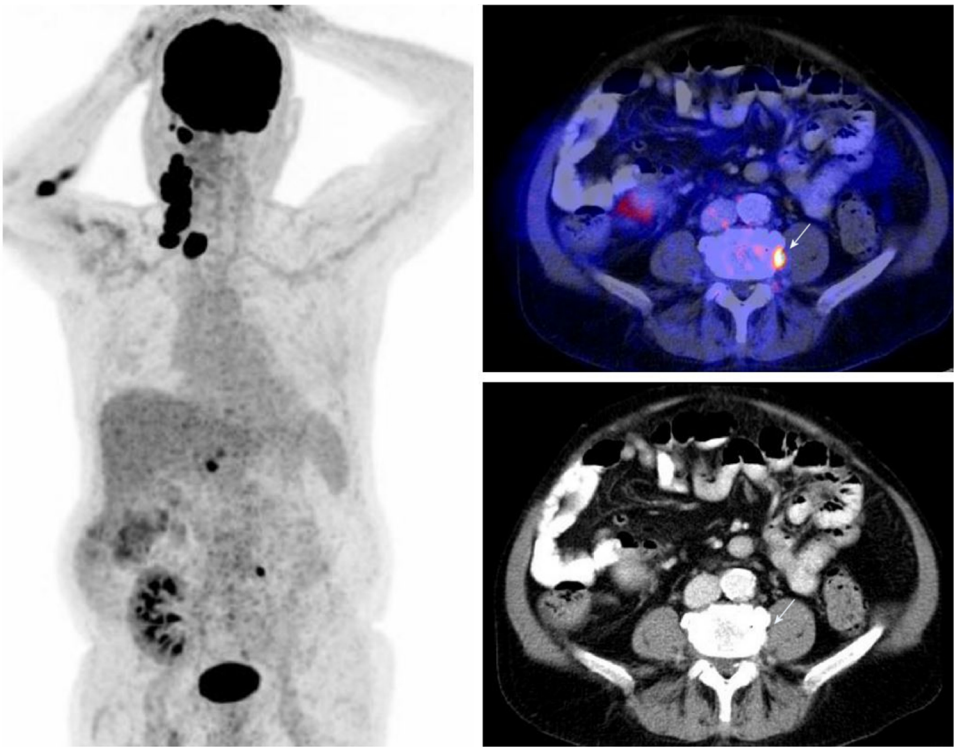

Fig. 3. 78-year old patient with monomorphic PTLD after kidney transplant. Maximum intensity projection (MIP) of FDG-PET reveals multiple metabolically active right cervical lymphadenopathies, a focal lesion in the omental foramen and a focal para-vertebral lesion at the left side (left image). Transaxial fused PET/CT of the pelvis shows a focal lesion with increased FDG uptake at the left para-vertebral area without noticeable lesion on CT (right image).

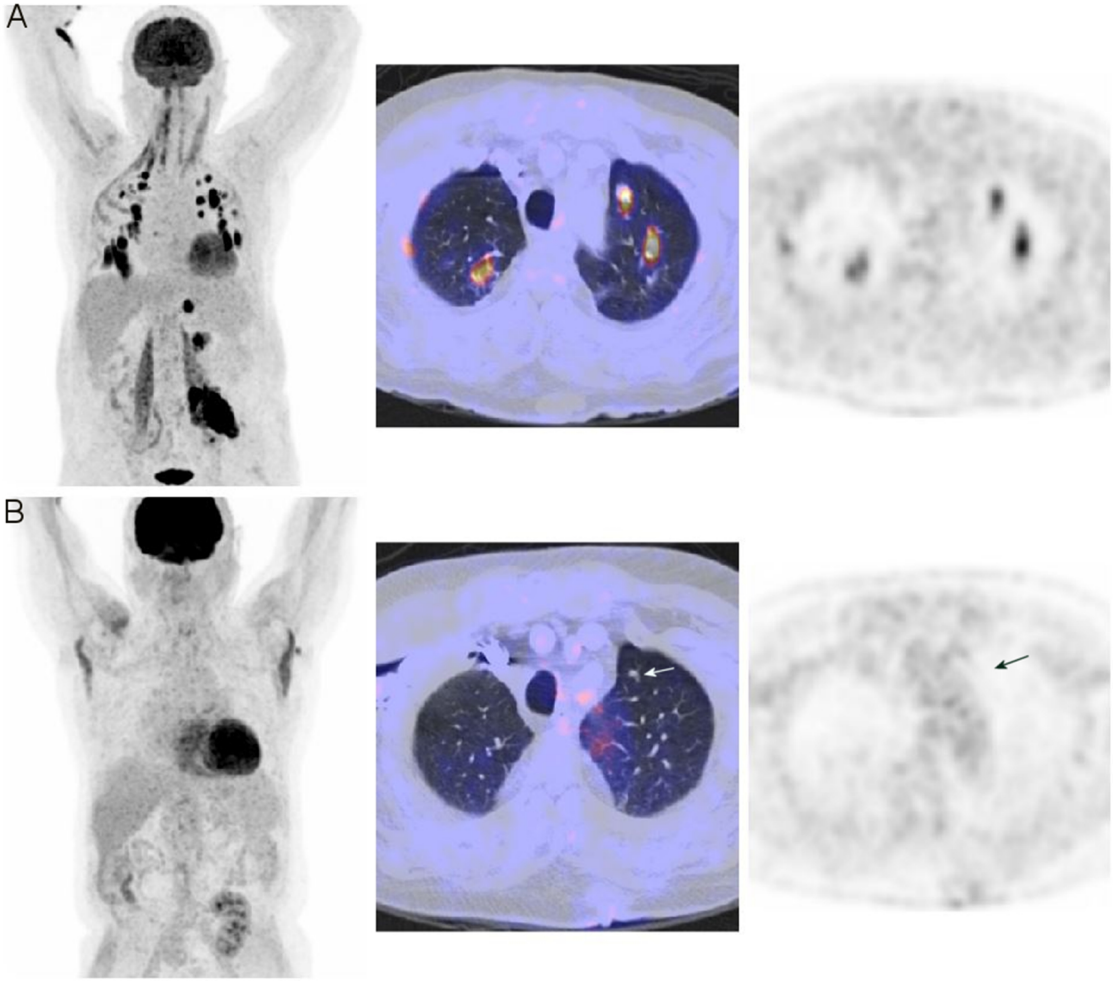

Fig. 4. (A) 62-year old patient with monomorphic PTLD after kidney transplant. Baseline maximum intensity projection (MIP) of FDG-PET reveals multiple metabolically active supra- and infra-diaphragmatic lymphadenopathies, multiple hyper-metabolic lesions in both lungs and a focal lesion in the left native kidney (left image). Transaxial fused PET/CT and FDG-PET images of the thorax showing two focal lesions in the left lung and a focal lesion in the right lung (middle and right image). (B) Patient after 8 cycles of rituximab. MIP FDG-PET reveals complete response (left image). Transaxial fused PET/CT and FDG-PET images show a remaining focal lesion in the left lung without any remaining FDG activity corresponding to a complete response (middle and right image).

eligible for this review, it remains a potentially feasible imaging modality for the staging and treatment response evaluation of PTLD (Schafer et al., 2014; Heacock et al., 2015; Afaq et al., 2017). In children where ionizing radiation is a greater concern, MRI may be a valid alternative to other imaging modalities. Particularly, the recent developed hybrid PET/MRI equipment is of great interest for this subgroup with a significant reduction in ionizing radiation (up to 73%) (Schafer et al., 2014; Heacock et al., 2015). Although some methodological issues remain with regard to attenuation correction in osseous structures and lungs, these may be solved in the near future, making PET/MRI a valuable alternative for staging and treatment response evaluation of lymphoma patients. To date, no reports have been published on the applications of PET/MRI in PTLD patients. Another novel development in the field of nuclear medicine is the use of targeted PET imaging. One of the main limitations of FDG-PET/CT is its nonspecific character, limiting differentiation between malignant lesions and other areas of increased glucose uptake such as inflammatory or infectious foci. Current studies indicate that targeted markers provide an attractive solution to this drawback. In pre-clinical studies, PARP1-targeted PET imaging was superior to FDG-PET/CT in differentiating malignant lesions from inflammatory conditions in syngeneic DLBCL mouse models (Tang et al., 2017). Additional research is also suggested on the role of FDG-PET/CT in the detection of bone marrow involvement in PTLD. Gheysens et al. suggested that FDG-PET/CT is an accurate tool to detect focal marrow involvement and may obviate the need for a bone marrow biopsy (Gheysens et al., 2016). Although some of the reviewed articles seem to confirm this statement, the currently available data does not permit a firm conclusion in this review (Panagiotidis et al., 2014; von Falck et al., 2007; O'Conner and Franc, 2005; Takehana et al., 2014; Vali et al., 2015). Finally, semi-quantitative measurements, ranging from SUVmax and SUVpeak to high order metrics may provide valuable clinical information and influence management in PTLD patients. Although SUVmax and SUVpeak are clinically well recognized quantification methods, large center studies are needed to precisely assert its clinical value in hematological malignancies, specifically PTLD (Weber, 2005). More recently, whole-body metabolic metrics, such as metabolic tumor volume (MTV) and total lesion glycolysis (TLG) have also been suggested to better reflect tumor burden in lymphoma patients (Berkowitz et al., 2008; Basu et al., 2014). In DLBCL patients, MTV has been identified as a possible prognostic factor and as a tool to improve risk stratification (Cottereau et al., 2016; Song et al., 2012). In another study, TLG was found superior to the International Prognostic Index in predicting overall survival and progression free survival in DLBCL patients treated with R-CHOP (Kim et al., 2013). Furthermore, the use of machine-learning algorithms and its application in radiomics may in the future enhance visual interpretation and pave the way to the development of personalized medicine (Carlier and Bailly, 2015; Cook et al., 2018).

7. Conclusions

At this moment, FDG-PET(/CT) is the most frequently used imaging modality in PTLD patients after solid organ and hematopoietic stem cell transplantation, showing promising results in the detection, staging and therapy evaluation. However, the limited number of relatively small studies with inherent methodological shortcomings prevents a firm conclusion on this topic. When interpreting an FDG-PET(/CT) scan, one must to be aware of eventual pitfalls, such as the occurrence of false negatives due to physiological high background activity and early lesions PTLD (non-destructive PTLD, WHO 2017) as well as false positives due to inflammatory conditions (Swerdlow et al., 2017). Although no studies are available, MRI is the recommended imaging modality in case of clinical suspicion of CNS involvement. Large multicenter prospective studies using the available imaging modalities in an homogenous PTLD patient population are warranted to allow performance comparison of advanced imaging modalities at diagnosis and treatment response evaluation of PTLD patients.

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All authors contributed to final analysis and writing of the manuscript.

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Conflict of interest

All authors declare that they have no conflict of interest.

Ethical approval

This article does not contain any studies with animals performed by any of the authors. All procedures performed were in accordance with the ethical standards of the institutional research committee and with the 1964 Declaration of Helsinki and its later amendments.

Appendix A. Supplementary data

Supplementary material related to this article can be found, in the online version, at doi:https://doi.org/10.1016/j.critrevonc.2018.09.007.

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